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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Barsoum *et al.*
Application No.: 10/618,299
Filed: July 11, 2003
For: **Method of Enhancing Delivery of a Therapeutic Nucleic Acid**

Confirmation No.: 6907
Art Unit: 1633
Examiner: Robert M. Kelly
Atty. Docket: 2159.0830001/EJH/SAS

Declaration of Michael Parr Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, Michael Parr, declare and state as follows:

1. I received my education at the University of British Columbia. My training continued at Harvard Medical School. A copy of my curriculum vitae is attached as Exhibit 1.

2. I am currently employed at Biogen Idec Inc., where I hold the position of Senior Scientist. My work involves the use of viral vectors for gene delivery.

3. I am familiar with the above-identified application and pending claims as well as the July 29, 2005 Office Action. I am also familiar with the Tao *et al.* reference discussed in this Declaration.

4. I have been told by attorneys for Biogen Idec Inc. that the specification of a patent application describes the claimed invention while the claims establish the scope of the invention. I understand that claims 1, 34-49, and 52-54 are directed to methods

and compositions for increasing the levels of a therapeutic gene product in a subject comprising the administration of agents that reduce uptake by Kupffer cells of viral vectors encoding therapeutic gene products and are also directed to methods for reducing toxicities associated with administration of virally encoded transgenes. I understand that the claims have been rejected in the Office Action for, among other things, lack of enablement. I have been told by attorneys for Biogen Idec Inc. that a specification is 'enabled' if it conveys to a person having ordinary skill in the art how to make and use the claimed invention. In my view, a "person of ordinary skill in the art" with respect to the above-identified patent application would be a person having at least post-doctoral level training and experience in the field of virally-encoded transgene delivery. Furthermore, I understand that:

(a) the Examiner acknowledges that the specification enables increasing the level of a therapeutic gene product in the liver of a subject by a method comprising a first adenoviral vector comprising a transgene encoding a therapeutic nucleic acid operably linked to promoter elements for expression in hepatocytes and a second adenoviral vector not comprising the transgene administered prior to or concurrently with the first adenoviral vector, with each vector administered to the liver by intravenous, intrapertioneal, or direct routes and for pharmaceutical compositions comprising such vectors and a pharmaceutically-acceptable carrier but

(b) the Examiner alleges that the specification is not enabling for, among other things, using any route other than intravenous, intraperitoneal, or direct

administration for delivery of a viral vector to liver tissue or for transformation of liver cells.

5. In making this declaration, I demonstrate that one of ordinary skill in the field of gene therapy as of January 22, 2001, the effective filing date of the present application, given the teachings of the specification, could have administered viral vector encoding a transgene by non-intravenous routes, and detect expression of the transgene in the liver.

6. Experiments were performed by me or under my direction which demonstrate that routes of administration other than intravenous administration result in expression in the liver of a transgene encoded by a viral vector.

7. Our data suggests that other routes of administration, such as subcutaneous (s.c.) injection, can result in dissemination of the vector to other sites within the body, and in particular, a distant organ such as the liver. The vector must travel via a systemic route (blood), and is therefore somewhat analogous to the traditional method of systemic administration (intravenous)(i.v.). Thus, agents which affect Kupffer cell uptake of systemically administered viral vectors would be expected to alter tissue transduction efficiency for the s.c. route of administration just as they have been demonstrated to do so for i.v. administration.

8. Figure 1 (attached herewith as Exhibit 2) illustrates the observation that a s.c. injection of an adenoviral vector can result in systemic distribution and result in liver expression of the vector's transgene, typical of what is seen with an i.v. administration of adenovirus.

9. In one set of experiments, 1 x 10^{11} viral particles of a first generation adenoviral vector (*See* Specification at page 12, lines 4-5, and page 13, lines 11-24) encoding the reporter transgene firefly luciferase (Ad.LUX) were injected subcutaneously into the flank of five nude mice. Twenty-one days after subcutaneous administration of viral vector encoding the transgene, the mice were injected with a substrate for luciferase, anesthetized 10 minutes later, and analyzed for photon output resulting from conversion of the substrate by the luciferase transgene product. Xenogen® imaging was utilized to detect total photon output associated with the subcutaneous injection site and the liver. As a control for liver expression, five additional mice were intravenously injected with the aforementioned viral vector and analyzed for total photon output at twenty-one days.

10. Figure 1 shows that s.c. administration of 1 x 10^{11} viral particles results in expression of the luciferase transgene in the liver. Kupffer cells have been shown to have a large influence on the level of transgene expression when low doses of viral vector are administered intravenously (*See, i.e.*, Tao *et al.*, *Mol. Thera.* *3*(1): 28-35 (2001).) Kupffer cells form a fixed barrier to liver parenchyma transduction, drastically reducing the efficiency of the observed liver expression at lower doses. Thus, agents which affect Kupffer cell activity would be predicted to have an even greater effect on other routes of administration where systemic distribution of the vector is observed but at a lower level than a straight i.v injection, such as the s.c. injection and liver expression shown here. Similarly, agents that reduce Kupffer cell uptake of viral vectors encoding transgenes would be predicted to have a significant effect on non-intravenous routes of administration where systemic distribution allows for distribution to the liver but at

proportionally lower levels than observed with intravenous administration which specifically targets the liver.

11. I further declare that the above statements made of my own knowledge are true and the above statements based on information and belief obtained from the references and documents discussed are believed to be true. Additionally, I declare that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Title 18 United States Code Section 1001, and that willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Respectfully submitted,

Michael Parr

Date: 1/27/06

CURRICULUM VITAE

NAME: Michael Jeffrey Parr

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PLACE OF BIRTH: Toronto, Canada, 01/23/68

CURRENT POSTION: **Senior Scientist**
Gene Delivery Group, Oncology
Biogen Idec, Inc.
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14 Cambridge Center
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SUMMARY:

- 15 years experience in a variety of therapeutic modalities
  - Ph.D. (UBC, Canada) in liposomal drug delivery systems
  - Post-doc (Harvard) in gene therapy
  - Industry (Biogen-Idec) (approaching 7 years); Research team leader on successful IND
- Extensive knowledge of preclinical animal models
- Rapid advancement of program from Research through Development to Clinic via efficient IND-enabling study designs
- Outstanding technical and supervisory capabilities
- Team oriented interactions across wide areas of company (Research, PreClinical, Medical/Clinical, Manufacturing, Legal, Commercial)
- Background in immuotherapies, oncology, gene delivery

OBJECTIVE:

Facilitate rapid and more efficient identification and development of novel therapeutic approaches from Research/Development to the clinic.

EDUCATION:

1995	Ph.D.	University of British Columbia, Vancouver BC (Biochemistry and Molecular Biology)
1990	B.Sc. Honours	University of British Columbia, Vancouver BC (Biochemistry)

HOSPITAL APPOINTMENTS:

1998-1999	Instructor in Medicine	Dana-Farber Cancer Institute Department of Adult Oncology Boston MA
1995-1998	Research Associate in Medicine	Dana-Farber Cancer Institute Department of Adult Oncology Boston MA

POSTDOCTORAL TRAINING:

1998-1999	Instructor in Medicine	Harvard Medical School Boston MA
1998-1999	Instructor in Medicine	Dana-Farber Cancer Institute Department of Adult Oncology Boston MA
1995-1998	Research Associate in Medicine	Harvard Medical School Boston MA
1995-1998	Research Associate in Medicine	Dana-Farber Cancer Institute Department of Adult Oncology Boston MA

PROFESSIONAL EMPLOYMENT:

2004 - present	Senior Scientist	Biogen Idec, Inc. Cambridge MA
2000 - 2004	Scientist II	Biogen, Inc. Cambridge MA
04/26/99-2000	Scientist I	Biogen, Inc. Cambridge MA

2005 CURRENT RESEARCH PROJECTS/RESPONSIBILITIES WITHIN BIOGEN IDEC (BIIB)

1. **Interferon Gene Delivery (Ad.hIFNβ) Phase I/II Clinical Program:**
   - Core Team Member - Lead Research Representative (includes Commercial, Manufacturing, Clinical)
   - Clinical Development Team Member - Lead Research Representative
   - IND author and editor, including dealing with FDA directly on biological/scientific issues

- CMC Team Member (manufacturing)
- CMC Assay Sub-team (characterization and release assay development for commercial lots)
- PCDS Assay Sub-team Member (preclinical, including NHP study design)
- Generated IND enabling data in preclinical mouse studies, namely developing and testing Ad.hIFNβ in a wide variety of tumor models, including standard s.c. xenografts, plus orthotopic models of liver metastasis of colorectal ca, prostate ca, ovarian ca, glioma - demonstrating both primary tumor elimination and immune mediated effects at a distance in syngeneic tumor models (metastatic models). Secondary goal of exploring alternative dosing/ safety mitigation strategies. Beginning chemocombo studies for re-defining PhII/III path with SOC.
- Leads Research evaluation of clinical samples (mRNA - RTPCR analysis of endogenous vs. transgene expression; cytokine ELISAs/multiplex bead analysis of immunotherapy response, etc. outside of standard clinical assays)
- Initial development and ongoing support for Research activities in improved vector (existing) design and implementation
- In-licensing/due diligence evaluations of novel vector technologies (oncolytic vectors, tumor targeting technologies) as next generation platforms for program.

2. **Gene Therapy Research Projects, Vector Design/Construction/Production/Purification**
   - Adenovirus, AAV, lentiviral vector technology
   - Large scale production/purification current stocks adenoviral stocks used in Research
   - Design/construction novel vector constructs (e.g. IRES/bicistronic vectors; adenoviral-mediated expression of antibodies, Fc-fusion proteins, RNAi)
   - Second generation anti-tumor vectors (e.g. other immune stimulatory gene products; tumor antigens)
   - Continued core vector technology development (large scale/commercial production/purification of adenovirus, AAV vectors); additional vector assay development (Q-PCR, HPLC, light scattering, analytical ultracentrifugation)

3. **Other Supporting Projects (Validation Models):**
   - Neurodegeneration: gene delivery for ALS, Macular Degeneration, Stargardt's Disease, Huntington's Disease
   - Oncology Small Molecule Development Team (TGFβ-Receptor Kinase Small Molecule Inhibitor): development of surrogate efficacy model using viral vectors as quick alternative to transgenic mice
   - Immunology biology: vectors to express or inhibit molecules in a variety of pathways

4. **Chair, IACUC (Institutional Animal Care and Use Committee)**
   - 2004, 2005 IACUC Chair
   - 2002-2005 Scientist representative member
   - Electronic Protocol Project development and launch
   - facility has approximately 100 active protocols across 30 different principal investigators, daily census of 16,000 mice and rats

5. **Tysabri Research Investigation Team**
   - Lead Virologist; research into PML, animal model development for long term studies into Tysabri and other neuro products and their effects on immune surveillance

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EXPERTISE:

Molecular Biology
: all current molecular biology techniques, including extensive use of PCR-based technologies, use of Affymetrix technology

Biochemistry
: standard protein biochemistry techniques

Tissue culture

extensive experience in cell line experimentation in a variety of assay formats; primary cell isolation/culture

Rodent Models/Surgery/Pharmacology
15 years experience in variety of animal models, including survival surgery, ectopic and orthotopic tumors, imaging technologies for tumor response, vector distribution, etc.

Oncology
cellular and immunological understanding of disease; MOA of wide variety of therapeutics

Viral Vector technology
extensive range of viruses as vectors; use in vivo; manufacturing, purification

Liposomal drug delivery vehicles (Ph. D.)
strategies for improving tumor accumulation of drug-loaded liposomes

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AWARDS AND HONORS:

1987-1988	Charles and Jane Banks Scholarship (UBC)
1988-1989	Dorothy and Arthur Holt Scholarship (UBC)
1991-1992	University Graduate Fellowship (UBC)
1992-1995	Medical Research Council (MRC) of Canada Studentship
1997-1999	American Brain Tumor Association (ABTA) Post-doctoral Research Fellowship
1997	Richard A. Smith Award, 1st prize, Dana-Farber Cancer Institute

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SUPERVISORY/TEACHING EXPERIENCE:

2005	Overall scientific and administrative oversight of 5-member Research Gene Delivery Team (also includes one other Senior Scientist and his Associate).
1999-2005	Two Associate Scientists direct reports (AS III - 5-8 years post Masters).
2002	Biogen Summer Intern Supervisor
2001	Biogen Summer Intern Supervisor
1995-1999	Training and supervision of 3 laboratory technicians (Dana-Farber, Harvard Medical School)
1993-1994	Undergraduate thesis supervisor (UBC)
1992-1993	Undergraduate laboratory teaching assistant (UBC)
1991-1992	Undergraduate thesis supervisor (UBC)

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Original Reports:

1. Tilcock CPS, Ahkong QF, Parr M. An improved method for the preparation of liposomal gadolinium-DTPA: ionophore mediated active entrapment of gadolinium. Inv. Radiology 1991; 26: 242-7.

2. Parr MJ, Bally MB, Cullis PR. The presence of GM1 in liposomes with entrapped doxorubicin does not prevent RES blockade. Biochim. Biophys. Acta 1993; 1169: 249-52.

3. Parr MJ, Ansell SM, Choi LS, Cullis PR. Factors influencing the retention and chemical stability of poly(ethylene glycol)-lipid conjugates incorporated into large unilamellar liposomes. Biochim. Biophys. Acta 1994; 1195: 21-30.

4. Longman SA, Tardi PG, Parr MJ, Choi LS, Cullis PR, Bally MB. Accumulation of protein coated liposomes in an extravascular site: influence of increasing carrier circulation lifetimes. J. Pharm. Exp. Therapeutics 1995; 275: 1177-84.

5. Dong Y, Wen P, Manome Y, Parr MJ, Hirshowitz A, Chen L, Hirschowitz EA, Crystal R, Weichselbaum R, Kufe DW, Fine HA. In vivo replication-deficient adenovirus vector-mediated transduction of the cytosine deaminase gene sensitizes glioma cells to 5-fluorocytosine. Human Gene Therapy 1996; 7: 713-720.

6. Parr MJ, Masin D, Cullis PR, Bally MB. Accumulation of liposomal lipid and encapsulated doxorubicin in murine Lewis Lung Carcinoma: the lack of beneficial effects by coating liposomes with poly(ethylene glycol). J. Pharm. Exp. Therapeutics 1997; 280: 1319-1327.

7. Parr MJ, Manome Y, Tanaka T, Wen P, Kufe DW, Kaelin WG, Fine HA. Tumor-selective transgene expression in vivo mediated by an E2F-responsive adenoviral vector. Nature Medicine 1997; 3: 1145-1149.

8. Parr MJ, Wen PY, Schaub M, Khoury SJ, Sayegh MH, Fine HA. Immune parameters affecting adenoviral vector gene therapy in the brain. J. Neurovirology 1998; 4: 194-203.

9. Lim HJ, Parr MJ, Masin D, McIntosh NL, Madden TD, Zhang G, Johnstone S, Bally MB. Kupffer cells do not play a role in governing the efficacy of liposomal mitoxantrone used to treat a tumor model designed to assess drug delivery to liver. Clin. Cancer Res. 2000; 6: 4449-4460.

10. Tao N, Gao G-P, Parr MJ, Johnston J, Baradet T, Wilson JM, Barsoum J, Fawell S. Sequestration of adenoviral vector by Kupffer cells leads to a non-linear dose response of transduction in liver. Mol. Ther. 2001; 3: 28-35.

11. Jakubowski A, Ambrose C, Parr M, Lincecum JM, Wang MZ, Zheng TS, Browning B, Michaelson JS, Baestcher M, Wang B, Bissell DM, Burkly LC. TWEAK induces liver progenitor cell proliferation. J. Clin. Invest 2005; 115: 2330 - 2340.

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Books:

1. Parr MJ, Cullis PR. Transbilayer transport induced by transmembrane pH gradients in liposomes: implications for biological systems, in Handbook of Non-Medical Applications of Liposomes, CRC Press Inc. Boca Raton, FL. Lasic DD, Barenholz, Yechezkel, eds. 1996.

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Abstracts and Presentations:

1. Parr MJ. Liposomes containing G_{M1} and entrapped doxorubicin induce RES blockade [oral]. 18th Annual Western Canada Biomembranes Conference, Whistler BC, December 4-6, 1992.

2. Parr MJ, Ansell SM, Choi LS, Cullis PR. Factors influencing the retention and chemical stability of poly(ethylene glycol)-lipid conjugates incorporated into large unilamellar liposomes [poster]. 3rd Liposome Research Days Conference, Liposomes: the Next Generation, Vancouver BC, June 19-22, 1994.

3. Parr MJ. Circulation Lifetimes and tumor accumulation of liposomal drug delivery systems [dissertation, Ph.D.]. Vancouver BC: University of British Columbia, October 1995.

4. Parr MJ, Masin D, Cullis PR, Bally MB. Sterically stabilized liposomal doxorubicin exhibits reduced passive tumor targeting efficiency (T_e) in mice bearing Lewis Lung Carcinoma (LLC) [poster]. 87th Annual Meeting of the American Association for Cancer Research, Washington DC, April 20-24, 1996.

5. Manome Y, Parr MJ, Tanaka T, Wen P, Kufe DW, Kaelin WG, Fine HA. Targeted gene expression in gliomas using an E2F-responsive adenoviral vector [oral]. Gene Thearpy Meeting, Cold Spring Harbor Laboratory, NY, September 25-29, 1996.

6. Parr MJ, Wen PY, Schaub M, Khoury SJ, Sayegh MH, Fine HA. Immune parameters affecting adenoviral vector gene therapy in the brain [poster]. 49th Annual Meeting of the American Academy of Neurology, Scientific Program, Boston MA, April 12-19, 1997.

7. Parr MJ, Manome Y, Tanaka T, Wen P, Kufe DW, Kaelin WG, Fine HA. Tumor-selective transgene expression in vivo mediated by an E2F-responsive adenoviral vector [poster]. Science Fair/Smith Prize Competition, Dana-Farber Cancer Institute. December 12, 1997.

8. Parr MJ, Manome Y, Tanaka T, Wen P, Kufe DW, Kaelin WG, Fine HA. Tumor-selective transgene expression in vivo mediated by an E2F-responsive adenoviral vector [oral]. Seminars in Oncology, Dana-Farber Cancer Institute. April 21, 1998.

9. Lim HJ, Parr MJ, Masin D, McIntosh NL, Zhang G, Bally MB. Liposomal anti-cancer drug delivery to the liver: defining the factors mediating therapeutic activity [abstract/poster]. J. Liposome Research 1998; 8: 79-80.

10. Parr MJ, Manome Y, Tanaka T, Wen P, Kufe DW, Kaelin WG, Fine HA. Targeted Gene Therapy in Gliomas in E2F-Responsive Adenoviral Vectors [poster]. 4th Biennial Brain Tumor Tumor Symposium/American Brain Tumor Association, Chicago IL, July 23-25, 1999.

11. Parr MJ, Tao N, Gao G-P, Wilson JM, Barsoum J, Fawell S. Strategies to Obtain Predictable, Linear Dose Response of Transgene Expression Following Systemic Administration of Recombinant Adenoviral Vectors [poster 148]. The 3rd Annual Meeting of The American Society of Gene Therapy, Denver CO, May 31 - June 4, 2000.

12. Parr MJ, Sanchez-Salazar J, Zarcone P, Barsoum J. Low Doses of Adenovirus-interferon-beta (Ad-hIFN-β) Result in Complete Regression of Pre-established Tumors Following Direct Injection in an Orthotopic Model of Prostate Cancer [poster]. The 4th Annual Meeting of The American Society of Gene Therapy, Seattle WA, May 30 - June 3, 2001.

13. Sanchez-Salazar J, Garber E, Barsoum J, Parr MJ. Expression of a an anticancer antibody via an adenoviral vector results in distant tumor regression and enhanced survival in mice [oral]. The 6th Annual Meeting of The American Society of Gene Therapy, Washington DC, June 4 - 8, 2003.

14. Sachs CW, Parr M, Chutkowski CT, Barsoum J, Chan C, Farman C, Walker M, Hutto D, Martin PL and Green JD. Preclinical safety of BG00001, a replication defective adenoviral vector expressing the human interferonβ (hIFNβ) gene, following intraporstatic dosing in rhesus monkeys. Toxicological Sciences Vol. 72 No. S-1, Abstract 1458, 2003.

15. Jakubowski A, Parr M, Thompson J, Ambrose C, Baetcher M, Linceccum J, Wang M, Crowell T and Burkly L. TWEAK overexpression promotes ductal and progenitor cell hyperplasia in the liver. EMBO Workshop on Liver Development, Gene Regualtion and Disease, June 14-19, 2003, Heraklion, Crete.